REMARKS

The Office Action has indicated that Claim 39 is free of the art. But it has rejected Claim 1 under 35 U.S.C. §112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Further, the Office Action has further rejected Claims 1 and claims dependent thereon under 35 U.S.C. §112, first paragraph, as allegedly being non-enabling. Finally, the Office Action has rejected Claims 1-8 under 35 U.S.C. §103(a) as defining subject matter, which is allegedly rendered obvious by the teachings in U.S. Patent No. 4,891,373 to Stoss ("Stoss"), U.S. Patent No. 5,665,766 to Byrne et al. ("Byrne et al."), U.S. Patent No. 6,858,632 to Molliner et al ("Molliner et al"), WO 2000/020420 in which Molliner et al. are inventor ("'420 application"), and WO/0303037 in which Nallet et al. are inventors (" 'Nallet et al.").

Applicants are submitting this Amendment, which when taken with the comments herein, are deemed to place the present case in condition for allowance. Favorable action is respectfully requested.

Applicants have cancelled without prejudice the non-elected subject matter, that is, Claims 9-17 and 34-38. However, applicants have not abandoned this subject matter therein and reserve the right to file a divisional application directed thereto.

Pursuant to the rejection of Claim 1 under 35 U.S.C. §112, second paragraph, the Office Action alleges that the term "prodrug" and "solvates" are vague and that the definitions of R^a is unclear.

Applicants respectfully disagree. The term "prodrug" is a term of art. Attention is directed to page 10, lines 6-22 of the instant specification wherein the term "prodrug" is defined. As defined, it includes, inter alia, esters, such as esters of amino acids, phosphate esters, metallic salts of sulfured.

Thus, prodrug includes any compound which, when administered in vivo, forms the compounds having Formula I. One of the ordinary skill can easily determine these compounds by identifying the metabolite thereof. For example, if a drug is administered to a subject and the metabolite has the structure of Formula I, then it is a prodrug and is encompassed within the scope of the present invention. Quite often, prodrugs can be recognized without actually identifying the metabolite. For example, attention is directed to the definition of prodrug described hereinabove, which provides examples thereof. Attention is also directed to Example 8, which describes a compound containing a hydroxyl substituent, which can be esterified, for example, it can be converted to a carbamate, by techniques known to one of ordinary skill in the art. These are examples of prodrugs, which can be cleaved to form compounds of Formula I by esterases found in humans. Thus, the scope of prodrugs is clearly defined in the application. Moreover, by reciting the term "prodrug" in the claims, there is no question that the prodrugs are within the scope of the claimed subject matter.

With respect to the definition of R^a, contrary to the allegations of the Office Action, the definition of R^a is not confusing. It is clear from the definition of R^a that the various R^a residues may be unsubstituted or substituted and if substituted contains the substituents listed on page 2 of Claim 1 (See lines 25-27 of Claim 1).

Thus, the metes and bounds of Claim 1 are well defined. Accordingly, the rejection of Claim 1 under 35 U.S.C. §112, second paragraph, is obviated. Withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 1-8 under 35 U.S.C. 3112, first paragraph, the Office Action alleges that the specification does not provide enablement of the claimed subject matter. Applicants disagree.

To substantiate the enablement of the present invention, applicants will analyze each of the factors presented in the decision of In re Wands 858 F2d, 731, 737, 8 USPQ2d, 1400, 1424 (Fed.Cir. 1988). Applicants will analyze enablement utilizing the definition of the level of skill in the art as described in the Office Action. It is to be understood that applicants are not necessarily adapting this criteria as the level of skill with respect to the present invention, however, applicants are utilizing this level of skill identified in the Office Action to comment on the analysis of the Office Action and to show that even using its analysis, the present application is enabling.

1. **The Breadth of the Claims**. The claims are not overlybroad, as they are restricted to compounds of Formula I, tautomer thereof prodrugs or solvates and pharmaceutically acceptable salt. There are only three variables in the structure n, X and R, each of which is defined in the claims. Each of the compounds encompassed by the claims is represented by a compound of Formula I or solvate or pharmaceutically acceptable salt or by a compound that metabolizes in vivo into compound I.

2. **The Nature of the Invention**. The invention, as entered, is directed to a compound of Formula I, tautomer, pharmaceutically salt thereof, prodrug or solvate.

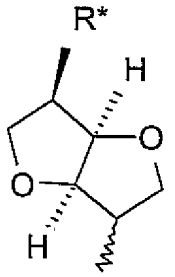
3. **The Level of Skill in the Art**. According to the Office Action, the level of skill of the art is high Although applicants do not necessarily adopt this characterization, if one accepts, pro arguendo, that the level of skill is high, then the skilled artisan is well aware of synthetic techniques described in the art for preparing various types of organic molecules ~~of different compounds,~~ including the syntheses described in various textbooks and treatises, including, for example, the textbook by Smith and March, "Advanced Organic Chemistry", 5th Ed., 2001, Wiley-Inter Science as well as the literature which describes general synthetic schemes for making various types of compounds. In addition, the skilled artisan is well aware of the various synthetic routes for preparing various groups in organic chemistry.

4. **The amount of direction provided and the presence or absence of working examples.** Since the level of skill is considered high the specification need not describe the details of making various types of bonds such as C-C, disulfides including unsymmetrical disulfides. For example, attention is directed to examples 8 and 11 of the instant specification which illustrate how to obtain asymmetric disulfurs, wherein

n is 0,

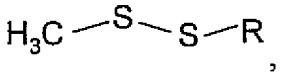
X is S,

R is Ra, wherein Ra is the group



and wherein R* is OH or acetyloxy.

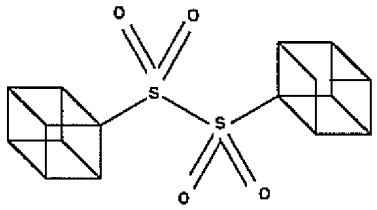
With respect to the rest of asymmetric disulfurs, i.e., those wherein Ra is a different group, the skilled artisan could easily obtain them using techniques which are routine to the skilled artisan. In fact, there are numerous examples described in conducting a search of asymmetric disulfur compounds. A search in SCIFINDER of simple asymmetric disulfurs for compounds having the following structure:



gives a result of about more than 1700 products. Reviewing these references, one of ordinary skill in the art could review the procedures for making same and based therein, provide a synthetic route for preparing non-symmetrical disulfur compounds. This would not require an undue amount of experimentation.

The same rationale is true with respect to compounds containing other groups, e.g., SO_2-SO_2 groups. Based on the knowledge of one of ordinary skill in the art as defined by the United States Patent and Trademark Office ("USPTO"), a person skilled in the art could prepare such bonds using routine techniques to obtain them. For example, a search in SCIFINDER reveals that 250 products with the disulfone structure are described in 125 citations.

The following disulfur group is, for example, described in Priefer, Ronny; Martinea, Eric; Harpp, David N.; Derivation of dicubyl disulfide, Journal of Sulfur Chemistry (2007), 28(6), 529-535. Code: JSCOFC ISSN: 1741-5993. DOG 148: 517167, AN 2007: 1227619 CAPLUS:



Using the techniques described therein, one can prepare a compound with two SO_2 groups bonded to each other without an undue amount of experiment.

The Office Action also alleges that the application is non-enabling with respect to making CH or C-C bonds. Again, applicants disagree. The skilled artisan is well aware of the literature for making these types of compounds. For example, reference is made to Example 8. The skilled art could have obtained such compounds with CH or C-C bond from the product of Example 8 by transforming the hydroxyl group into a halogen (C-halogen), or by a hydrogenolysis process, which yields a product with C-H. Finally, the linking reaction catalyzed with "Pd" would result in products with C-C.

The Office Action refers to the various reaction schemes in the application as of academic nature and dismisses them summarily as failing to provide sufficient information to enable the compounds of the present invention. Applicants disagree. These are reaction schemes for preparing the compounds falling within the scope of Claims 1 et seq. These reaction schemes are described in terms of the chemistry for the chemical reactions provided. One of ordinary skill in the art, as defined by the Office Action, can refer to treaties, textbooks, or literature to find the chemistry for each of the

step in the recitation schemes or he may very well be familiar with the process for effecting each step of these conversions. For example, oxidizing agents are mentioned without specifying them because one of ordinary skill in the art recognizes the ehcmistry and is familiar with the oxidizing agents to be utilized. Moreover, resort can be made to the examples of the instant specification. In the examples, for instance, commercial products are mentioned (like Example 4 uses sodium periodate as an oxidizing agent). Nevertheless, one of ordinary skill in the art, as defined by the USPTO knows how to prepare them with many other oxidizing agents (See, e.g., Michael B. Smith and Jerry March "Advanced Organic Chemistry", Fifth Edition, 2001, Wiley Inter-Science, Chapter 19, page 1541.

As described, "When it is desired to obtain one of the diastereomers of sulfoxides it is preferable to carry out an enantioselective oxidation using one of the general methods described in the literature such as:

- Cellular cultures
- Enzymatic synthesis
- Oxidative systems with non-metals (iodinated compounds)
- Use of chiral phosphoryl chlorides
- Use of oxaziridines
- Chiral metallic complexes-catalyzed enantioselective oxidations"

All of these are known methods, especially the use of chiral metallic complexes-catalyzed enantioselective oxidations. There is a plenty of literature on asymmetric oxidations catalyzed by metallic complexes. The majority of systems are modifications of the Sharpless epoxidation reaction with titanium isopropoxide and diethyltartrate as chiral complexing catalyst using an oxidizing agent such as tert-butylhydroperoxide, processes which are known to one of ordinary skill in the art.

The Office Action also alleges that one of ordinary skill cannot make prodrugs or solvates. Applicants again disagree. Prodrugs, for examples, the prodrugs listed on Page 10, can be made by the skilled artisan without an undue amount of experimentation utilizing routine techniques. In addition, solvates are prepared by art recognized techniques.

With respect to the use of the compounds, attention is directed to page 14 et seq. of the instant specification which describes the preparation of various types of pharmaceutical formulations, which are prepared by well recognized art techniques and are known to one of ordinary skill in the art. In addition, attention is directed to page 15, lines 18 to page 16, line 29 of the instant specification, which describes how to administer the compounds of the present invention and the dosage amounts to be administered.

The Office Action alleges that applicants have not provided biological tests to show the efficacy. Applicants respectfully disagree. Applicants have provided data which support the utility alleged in the instant specification. For example, attention is directed to pages 43 et seq, which provides a showing with several representative examples, of the ability of compounds of Formula I to be a vasorelaxant (Table 1), to inhibit aggregates of platelets (Table 2), to inhibit platelet and monocyte adhesion to human endothelial cells (Tables 3 and 4), to inhibit LDL transcytosis in human microvascular endothelial cells (Table 5), to inhibit of LDL oxidation (Table 6) and to inhibit plasma oxidation (Table 7).

There is also in vivo data using representative compounds of the present invention. See, for example the sections entitled, the "Preventive and curative effect on

atherogenesis in rabbits fed on high cholesterol diet", described on pages 50-53 and the "Preventive and curative effect on atherogenesis in apo E-deficient mouse" on pages 53-55 and the "In vivo antithrombotic effect" on pages 55-57 of the instant specification. In addition, attention is directed to the discussion on page 60 of the instant specification, regarding in vitro protection against the cytotoxicity induced by oxygen radicals in HOVEC cells, using representative compounds of Formula I. The application also provides data which illustrate the in vivo protection against ischemia-reperfusion in the heart using representative compounds of the present invention (See pages 61-62). Thus, applicants have provided data to support utility.

The Office Action does not believe that the compounds of Formula I have the requisite utility. However, the Office Action has the initial burden to establish a reasonable basis to question the enablement for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1515 (Fed. Cir. 1993). It has not met its burden in this case. Case law has held that the specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for an enabling support. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the Marzocchi Court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is

inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

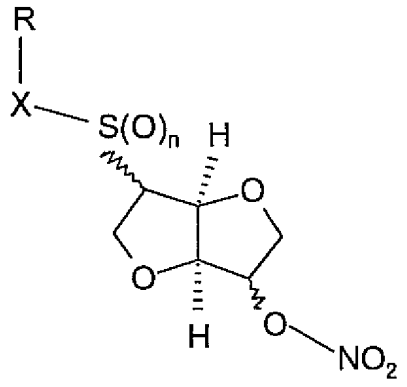
Here, the Office Action has not provided any rationale supporting its allegation that the full scope of the present invention is not enabled. In particular, the Office Action has not cited any reference, which refutes the teaching of the present invention. Moreover, the Office Action has not provided any evidence, which disputes the allegation of the utility of the present invention. The Office Action just renders a mere conclusion without providing any evidence whatsoever that shows that the present invention does not work. Without such a showing, the Office Action has not met its burden and has not make out a prima facie case of lack of enablement.

5. **The Quantity of Experimentation Needed to use the Invention**. Thus, based upon the teachings in the present invention and the knowledge of one of ordinary skill in the art, as described above, the specification provides sufficient information for one of ordinary skill in the art to make and use the compounds of the present invention without an undue amount of experimentation.

Therefore, for the reasons provided herein, the rejection of the claims under 35 U.S.C. §112, first paragraph is obviated; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 1-8, under 35 U.S.C. §103, the Office Action cites Stoss, Byrne et al., Molliner et al. and the `420 application and Nallet et al.

The claimed subject matter is directed to compounds of the formula (I) or a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof:



(1)

wherein

n is an integer of 0, 1, or 2

X represents $-S(O)_m-$, -(C=O)- or a single bond, wherein m is an integer of 0, 1, or 2, with the proviso that when X represents -(C=O)-, then n is 0,

R represents hydrogen or is a residue R^a, which residue R^a is selected from the group consisting of:

C_{1-6} alkyl;

C_{2-6} alkenyl;

C_{3-8} cycloalkyl;

C_{3-8} cycloalkyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;

C_{4-8} cycloalkenyl;

C_{4-8} cycloalkenyl, wherein one CH_2 group is replaced by O, S, N or NCH_3;

phenyl;

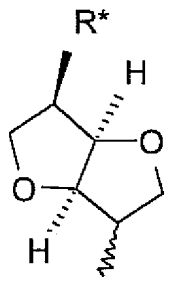
pyridyl;

thiophenyl;

nitrosyl;

S-cysteinyl;

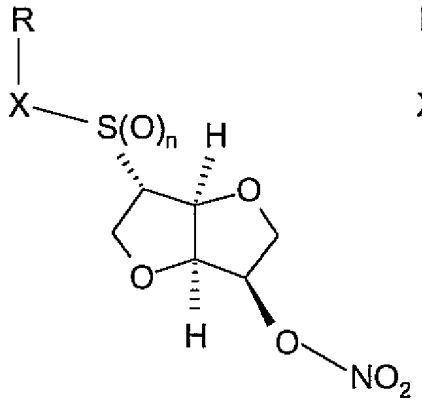
S-glutathionyl; and



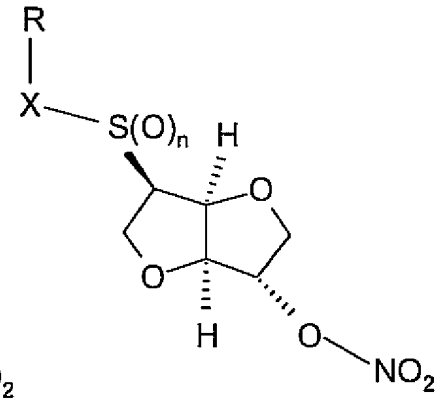
wherein R* is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl,, C_{3-8} cycloalkyl; C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen,

wherein R^n optionally is substituted by one to three groups independently selectd from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen,

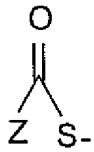
provided that when $RXS(O)_n$- and $-ONO_2$ are trans to each other with respect to the ring plane as depicted in formulae (Ia) and (Ib):



(1a)

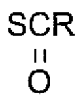
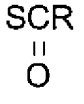


(1b)

then $RXS(O)_n$- does not represent  wherein Z is an C_1-C_4 alkyl group, aryl group, or an aralkyl group.

Byrne et al. and Stoss and Nallet et al. disclose isosorbide-5-mononitrates wherein the 2-position is substituted with O. They do not teach, disclose or suggest compounds wherein a S or $S(O)_n$ X R is present in the 2-position, as claimed. Moliner et al. disclose isosorbide mononitrate wherein the 2-position may be substituted with SC(O)R, wherein R is C_1-C_4 alkyl, aryl, aralkyl or 2-(R^1S)-pyridyl.

However, Moliner et al. and the `420 application disclose compounds wherein A and B are trans to one another where ONO_2 is at one position and the other position is ZC(=O)R, wherein Z is S. Such compound is not within the scope of the claims of the present invention.

The combination of references would suggest at most compounds wherein the 2-position is ONO_2 and the 5-position is S-C(O)R, whereby these two substituents are trans to one another. Based on the prior art, there is no reason to modify the 5-position with sulfur containing substituents; the teaching in the art refers to a 5-position being O or  ; it does not teach, disclose or suggest a sulfur atom there except as indicated above. Moreover, if a sulfur is present at the 5-position, the combination of references in the prior art suggest that it must be  and it must be trans to NO_2. This is not within

the scope of the present invention. Thus, the combination does not teach, disclose or suggest a compound of the present invention wherein the 2-position is ONO_2 and the 5-position is $S(O)_n$ X R, as claimed.

Thus, for the reasons provided, this rejection is overcome; withdrawal therefore is respectfully requested.

Thus, in view of the Remarks herein, it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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